A STUDY OF HEPATIC FUNCTION IN MAN BEFORE AND AFTER PARTIAL RESECTION OF LIVER

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It is well known that "liver-function tests" may be negative in the presence of extensive liver disease and that sometimes one of these tests may be positive whilst others are negative. Recently the opportunity arose of investigating liver function in a patient before and after partial resection of the liver, and the findings are recorded as an indication of the effects of simple reduction of liver tissue on these tests. In a survey of the literature recording partial hepatectomy in man we have

It was at this stage that the initial pathological investigations were carried out.

At a second operation for radical excision of the growth, also performed by Mr. Riddell, under thiopentone, curare, and nitrous oxide anaesthesia, the left lobe of the liver was removed by diathermy incision after ligation of the main vessels to the lobe. The excised portion of liver had a fresh weight of 215 g., and, like the organ as a whole, it showed no evidence of cirrhosis either macroscopically or microscopically. The remaining neoplastic nodule had a diameter of 1 cm.

During the immediate post-operative period, which was free from complications, the liver-function tests were all repeated.

The patient has remained well and gained weight during the nine months since his operation. There has been some increase in the size of the right lobe of the liver, presumably as a result of compensatory hyperplasia.

Method of Study

The following tests were performed before and after resection of the left lobe of the liver: (1) Tests related to protein metabolism: serum proteins, serum flocculation

TABLE I.—Results of Tests

Test	Pre-resection Results		Post-resection Results			
	Days Pre-op.	Pre-operative Results	Days Post-op.	Immediate Post-operative Results	Days Post-op.	Late Post-operative Results
Serum proteins	14	Total 5.4 g.%; albumin 3.5 g., globulin 1.9 g. A/G 1.8	5	Total 5.5 g.%; albumin 3.9 g., globulin 1.6 g. A/G 2.4	54 108	Total, 7.7 g.%; albumin 4.4 g., globulin 3.3 g. A/G 1.3 Total, 8.0 g.%; albumin 5.1 g., globulin 2.9 g. A/G 1.8
Colloidal red	14	Negative (0)	5	Positive (+ +)	54 108	Weak positive (+) Weak positive (+)
Cephalin cholesterol ..	14	Negative (0)	5	Very weak positive (±)	54 108	Negative (0) Negative (0)
Thymol turbidity and flocculation	14	5 units with flocculation	5	10 units with flocculation	54 108	8 units with flocculation 7 units with flocculation
Plasma prothrombin concentration	14	91% of normal	5	91% of normal		
Plasma amino-acid pattern ..	7	Normal	3	Abnormal, but typical of post-operative state		
Urine amino-acid pattern ..	14	Slight abnormality—probably legacy of first operation	1-7	" " "		
Blood urea	7	39 mg./100 ml.	5	39 mg./100 ml.		
Serum bilirubin	5	Direct, negative; indirect, 0.4 mg./100 ml.	5	Direct, negative; indirect, 0.4 mg./100 ml.		
Urine urobilin(ogen) ..	7	Normal	1-7	Excess on days 2-7. Peak excretion on 6th day		
Hippuric acid synthesis* (intravenous test)	6	Excretion in 1 hour, 0.64 g.	12	Excretion in 1 hour, 0.76 g.		
Bromsulphthalein clearance (dose 5 mg./kg.)	10	Retention at 1 hour, less than 2%	7	Retention at 1 hour, less than 2%		
Serum alkaline phosphatase ..	5	6 King-Armstrong units/100 ml.	5	4.5 King-Armstrong units/100 ml.		
Urea clearance	1	C _s = 81% and 70% of average normal				

* Normal excretion corrected for body weight (Scurry and Field, 1943) = 0.70-1.25 g.

been unable to find biochemical studies similar to those here recorded, and Berman (1951) does not mention such an investigation. However, Grey Turner (1923) recorded faecal fat, urinary ammonia, and urinary urea findings two years after resection of a hepatoma in a boy aged 13.

Case Report*

A man aged 54 was admitted to hospital with acute abdominal pain, and at a laparotomy performed by Mr. A. G. Riddell two nodules were found in the left lobe of the liver, from one of which haemorrhage was occurring. The bleeding nodule was excised and haemostasis was secured. Histological examination of the biopsy specimen showed it to be a primary liver-cell carcinoma, bile pigment being present in the neoplastic cells; there was no evidence of cirrhosis in the surrounding liver tissue.

*A separate communication describing the surgical procedure followed and the pathological features of the tumour is being prepared by Mr. A. G. Riddell.

tests (colloidal red, cephalin cholesterol, thymol turbidity, and flocculation), plasma prothrombin concentration, plasma and urinary amino-acid patterns, blood urea. (2) Tests related to bile-pigment metabolism: serum bilirubin, urinary urobilin(ogen). (3) Tests related to detoxicating function: hippuric acid synthesis (intravenous test). (4) Tests related to excretory function: bromsulphthalein clearance, serum alkaline phosphatase.

These tests were carried out by standard techniques in common usage. The methods employed in the case of the amino-acid studies, however, require mention. The concentration of individual amino-acids was followed by the method of paper partition chromatography, two-way chromatograms being run as described by Dent (1947). In testing urines for a pathological output of amino-acids a urine volume with a constant amount of total nitrogen—that is, 250 µg.—was used (Dent, 1949). In the case of plasma a constant volume of 625 µl. of ultrafiltered and desalted fluid was taken. Each specimen of urine and plasma was examined—oxidized and unoxidized.

The results are summarized in Table I.

Discussion

It is important in considering the results to estimate the proportion of liver tissue that was removed. Using the formula of Scurry and Field (1943)—namely, liver weight = 0.433 oz./lb. body weight—the theoretical liver weight calculated on the patient's maximum known weight is, in this case, 1,380 g.; hence about 16% of the organ was removed.

Before the results of some of the tests are discussed certain points applicable to the interpretation of all must be mentioned. First, there is the enormous functional reserve of the liver. Secondly, there is the remarkable speed of regeneration. In the rat, after removal of over 60% of the organ regeneration is complete in 10 to 21 days (Warner, 1938; Abercrombie and Harkness, 1951). Whilst it is probable that the rate of regeneration will be slower in a man of 54 years this factor may have played a part in the normal post-resection results. Finally, it must be remembered that in this case the primary carcinoma developed in a non-cirrhotic liver. In adults this is a circumstance of great rarity (Counsellor and McIndoe, 1926; Tull, 1932; Boyd, 1944; Hoyne and Kernohan, 1947; Willis, 1948; Mallory, 1948; Berman, 1951).

The further discussion is here confined to those tests which showed a significant change after the resection.

Serum Proteins

The initial estimation showed a rather low total protein. This low reading may well have been a result of the haemorrhage, despite a transfusion of 4 pints (2.27 litres) of blood after admission. The very much higher results found at follow-up are probably to be attributed to the replacement of the serum proteins lost at the time of the haemorrhage.

Serum Flocculation Tests

The thymol test alone registered an abnormality before the resection; moreover, the occurrence of flocculation in this reaction is stated to indicate abnormal liver function (MacLagan and Bunn, 1947; Neeffe *et al.*, 1950). Possibly this result is to be attributed to the presence of the carcinoma.

It can be seen (Table I) that in the immediate post-operative phase the colloidal-red and cephalin-cholesterol flocculation tests changed from negative to positive and that the thymol turbidity registered a greater degree of abnormality. Whilst the cephalin-cholesterol test had returned to normal in two months the colloidal red and thymol turbidity were still abnormal three months after operation.

In order to ascertain that the changes in the flocculation reactions were related to the liver resection, control tests were performed. These control observations were carried out on two cases of carcinoma of the pancreas, both found at laparotomy to have hepatic metastases, and on a case of carcinoma of the oesophagus subjected to radical surgery. A further control observation was made on a case in which a pedunculated secondary carcinoma of the liver, weighing 125 g., was excised. In all four the flocculation tests were negative one week after operation.

There is the possibility that the initial results may have been altered by dilution of the gamma globulin following transfusion. However, in the case of the post-resection results the dilution factor must again be taken into consideration, as the patient received a further 2 pints (1.14 litres) of blood during the operation. A change in these tests means in effect that there has been a qualitative change in the serum proteins—in the globulin or the albumin fraction, or in both. In clinical terms, such a change is less likely to be due to a reduction in liver mass than to a necrosis of liver cells. There would be ample opportunity for such to occur locally, both from the use of the diathermy knife and the ligation of the vessels to the left lobe, with the consequent disorganization of the intrahepatic circulation. However, the amino-acid studies gave no indication of necrosis. Thus it is of interest that Popper *et al.* (1949) believe that the thymol test remains positive during regeneration and distorted reconstruction of the liver.

Plasma and Urinary Amino-acid Patterns

It has been reported (Dent and Walshe, 1951) that certain changes are commonly found in the urinary excretion of amino-acids after abdominal surgery, particularly if the liver or biliary tract is involved. The initial chromatograms, following the first operation, showed minor abnormalities that do, in fact, fall within this category. After resection of the left lobe of the liver much greater alterations in amino-acid excretion were expected, because of the major disturbance in hepatic circulation and the necrosis that must have been produced. This was not the case, and only the usual post-operative response was observed. Figs. 1 and 2 show the patterns detected in the urine and plasma on the third post-operative day. The changes in the plasma were no more striking than those in the urine, the only abnormality being a definite rise in the cystine concentration. These findings accord well with those of Ferrari and Harkness (1951), who made similar studies on the rat after removal of two-thirds of the liver. In view of the dramatic rise of liver ethanolamine phosphoric acid reported by these workers as occurring 24 hours after operation, it is of some interest that our patient was excreting this compound, as the principal ninhydrin reactor in his urine, six months after operation. One further abnormality appears to merit attention

FIG. 1.—Diagram of a chromatogram from urine with a nitrogen content of 250 µg. oxidized. Specimen collected on the third post-operative day.

FIG. 2.—Diagram of a chromatogram from 625 µl. of plasma ultrafiltrate oxidized. The plasma was collected on the third post-operative day.

KEY.—1 = Tyrosine. 2 = Tryptophan. 3 = Phenylalanine. 4 = Leucine. 5 = Valine. 6 = α -Amino-butyric acid. 7 = "T" spot.* 8 = Proline. 9 = Arginine. 10 = Lysine. 11 = Alanine. 12 = Glutamine. 13 = Taurine. 14 = Serine. 15 = Glycine. 16 = Glutamic acid. 17 = Cysteic acid (from cystine). 18 = Unknown.
* "T" spot has since been identified as β -amino-isobutyric acid. (Crumpler, H. R., Dent, C. E., Harris, H., Westall, R. G., *Nature, Lond.*, 1951, 167, 307).

—that is, the presence of a ninhydrin reactor (Fig. 1, symbol 18) not reported by Dent (1948) as occurring in human urine. Work on the isolation and identification of this compound will form the basis of a separate communication. In conclusion it can be said that resection of 16% of the liver produced no specific change in amino-acid metabolism.

Urinary Urobilin(ogen)

Before resection the excretion was within normal limits. During the eight days immediately following operation the excretion was excessive on five days, the peak being reached on the sixth day. This was in fact a quantitative change in the excretion of urobilin(ogen), as allowance was made for variations in the 24-hour urine volumes. Control observations were made on eight cases following surgery of comparable severity. The results are shown in Table II. Reference to this

TABLE II

Operation	Pre-op. Day	Post-op. Days							
		1	2	3	4	5	6	7	8
Part. hepatectomy	—	—	+	+	0	++	+++	++	—
Part. gastrectomy	—	0	—	—	—	—	—	—	—
Lobectomy	—	—	—	—	—	—	—	0	—
Thoracoplasty	—	0	0	—	+	+	++	0	—
Laminectomy	—	0	—	—	—	—	—	—	—
Oesophagectomy	—	—	—	—	++	+++	++	0	—
Cholecystectomy	—	—	—	—	—	—	—	—	—
(without biliary drainage)	—	+	—	—	—	—	—	—	—
Blood transfusion (3 pints)	—	—	—	—	—	—	—	—	—

0, no specimen; —, no excess urobilin(ogen); +, slight excess; ++ moderate excess; +++, marked excess.

table shows that, while several of the controls did have excess urobilin(ogen) excretion post-operatively, in none was it manifest so early or so markedly as in the patient subject to partial hepatectomy. It seems possible, therefore, that part of this increase is directly attributable to decrease of liver mass available for disposal of the chromagen arriving via the portal vein.

Further control observations on a patient who received a transfusion of 3 pints (1.7 litres) of blood established that this alone was not likely to be responsible for the increased urobilin(ogen) in the urine following the resection.

Summary and Conclusions

Liver-function tests were performed before and after resection of 16% of the liver in a case of primary liver-cell carcinoma occurring in a non-cirrhotic organ.

The serum flocculation tests and the urinary excretion of urobilin(ogen) alone showed changes believed to be attributable to partial resection of the liver.

The serum proteins and the pattern of amino-acids in the blood and urine showed changes which are believed to be non-specific in relation to the operation.

The following tests failed to register the surgical intervention: plasma prothrombin concentration, blood urea, serum bilirubin, hippuric acid synthesis, bromsulphthalein clearance, serum alkaline phosphatase.

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REFERENCES

- Abercrombie, M., and Harkness, R. D. (1951). *J. Physiol.*, **113**, 7P.
 Berman, C. (1951). *Primary Carcinoma of the Liver*. Lewis, London.
 Boyd, W. (1944). *Pathology of Internal Diseases*. Kimpton, London.
 Counsellor, V. S., and McIndoe, A. H. (1926). *Arch. intern. Med.*, **37**, 363.
 Dent, C. E. (1947). *Biochem. J.*, **41**, 240.
 — (1948). *Ibid.*, **43**, 169.
 — (1949). *Biochem. Soc. Symposia*, No. 3, p. 34.
 — and Walshe, J. M. (1951). *Ciba Foundation Conference on Liver Injury*. Churchill, London. In press.
 Ferrari, V., and Harkness, R. D. (1951). *J. Physiol.*, **113**, 27P.
 Hoyne, R. M., and Kernohan, J. W. (1947). *Arch. intern. Med.*, **79**, 532.
 MacLagan, N. F., and Bunn, D. (1947). *Biochem. J.*, **41**, 580.
 Mallory, T. (1948). *New Engl. J. Med.*, **238**, 26.
 Neefe, J. R., Gambescia, J. M., Gardner, H. T., and Knowlton, M. (1950). *Amer. J. Med.*, **8**, 600.
 Popper, H., Steigmann, F., Meyer, K. A., Kozoll, D. D., and Franklin, M. (1949). *Ibid.*, **6**, 278.
 Scurry, M. M., and Field, H. (1943). *Amer. J. med. Sci.*, **206**, 243.
 Tull, J. C. (1932). *J. Path. Bact.*, **35**, 557.
 Turner, G. Grey (1923). *Proc. roy. Soc. Med.*, **16** (Sect. Surg.), 43.
 Warner, E. D. (1938). *J. exp. Med.*, **68**, 831.
 Willis, R. A. (1948). *Pathology of Tumours*. Butterworth, London.

BONE DYSTROPHY IN ASSOCIATION WITH MUSCULAR DYSTROPHY (MYOPATHY)

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In 1905 Professor Spiller stated that implication of the bones in progressive muscular dystrophy was not often observed, and that many of the textbooks on nervous diseases made no mention of it. This statement is almost as true now as it was then, and, although bone changes in poliomyelitis, syringomyelia, and other neuromuscular disorders are frequently described in standard textbooks, their association with primary muscular dystrophy is rarely mentioned.

Marie and Crouzon (1903) reported a case of muscular dystrophy with fracture and atrophy of the humerus. Spiller (1905), in an account of a case of muscular dystrophy with wasting of the humerus scapula, and acromion process, gave as his earliest reference that of Lloyd (1884); however, Friedreich had discussed the subject at length in 1873 and had referred to an earlier observation of Le Gendre.

Bone changes mentioned in the literature include not only kyphoscoliosis and deformities of the skull, foot, and pelvis, but also atrophy of the clavicles, scapulae, ribs, and innominate bones, and atrophy, narrowing, and, less frequently, shortening of the long bones. The latter have often a shaft of reduced width, the reduction of the medullary canal being more marked than that of the cortex, whereas the epiphyses may be of normal diameter, giving an attenuated dumbbell shape to the affected long bones. Zellweger (1946) described five patients whose pelves were x-rayed, and who were said to have coxa valga; one was shown to have bilateral dislocation of the hips with hypoplasia of the acetabula.